4. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists alleviates the symptoms associated with an immune disorder selected from the group consisting of multiple sclerosis, lupus, rheumatoid arthritis, scleroderma, insulin-dependent diabetes and ulcerative colitis.

B2 5. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists is derived from myelin basic protein.

6. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists is derived from proteolipid protein.

7. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists is derived from myelin basic protein and from proteolipid protein.

REMARKS

I. Rejection of Claims 1-7 Under 35 U.S.C. §103

A) Claims 1-7 Are Not Obvious Over Kuchroo, Karin, And Bona Because There Is No Motivation To Combine the Cited References

Claims 1-7 were rejected by the Examiner, on the assertion that they were obvious over Bona et al. in view of Kuchroo et al. and Karin et al. As discussed below, the present invention is not obvious over the cited combination of references.

In order for a combination of references to render an invention obvious, the references must provide motivation to create the claimed invention. The cited references do not provide motivation to create the claimed invention because they do not describe or suggest compositions comprising a T cell receptor antagonist and an immunoglobulin or portion thereof.

In general, the references discuss either the use of an immunoglobulin to deliver a known antigen for generating an immune response against that antigen, or they disclose T cell receptor antagonists. However, absent hindsight, there is no suggestion or motivation to substitute a T-cell receptor antagonist for an antigen in the prior art vaccine disclosures.

Kuchroo *et al.* (Journal of Immunology 153: 3326-3336) discloses T cell receptor antagonists comprising residues 139-151 of the myelin proteolipid protein. However, there is no disclosure or suggestion in this reference of linking the T cell receptor antagonist to an immunoglobulin or portion thereof.

Likewise, Karin discloses T cell receptor antagonists derived from myelin basic protein. However, the molecules disclosed in Karin are not linked to an immunoglobulin or portion thereof. Thus, there is no mention or suggestion in Karin of T cell receptor antagonists or compositions comprising a T cell receptor antagonist linked to an immunoglobulin or portion thereof.

Bona *et al.* focuses on antibodies having antigens inserted therein. There is no disclosure or suggestion in Bona *et al.* of inserting T cell receptor antagonists into an antibody.

Because the combination of the above references does not disclose or suggest compositions comprising a known T cell receptor antagonist linked to an immunoglobulin or a portion thereof, the claimed invention is not obvious over the cited combination of references.

B) The Claimed Invention Is Not Obvious Over The Cited References Because The Claimed Invention Provides Unexpected Results

Furthermore, the claimed compositions provide unexpected results which are not disclosed or suggested in the cited references. In particular, the claimed compositions prevent T cell activation (see specification at page 16, line 31). As indicated by the Declaration of Habib Zaghouani submitted herewith, the claimed compositions, when administered to subjects suffering from an autoimmune disease, permanently eliminated the symptoms of the disease in all the subjects treated with the compositions by preventing T cell activation. As discussed below, these results would not be expected from the disclosures of Bona, Kuchroo, and Karin.

In contrast to the permanent elimination of disease symptoms in all of the sick subjects treated with the claimed compositions, the experiments of Kuchroo involved coinjecting healthy animals with a self antigen and a T cell antagonist peptide (as opposed to the immunoglobulins containing a T cell antagonist therein used in the experiments described in the accompanying Declaration) to monitor the development of disease symptoms. Although the procedures of Kuchroo slowed the development of autoimmune disease in healthy animals, half the treated animals in Kuchroo developed autoimmune disease after 25 days (see the lower panel of Figure 4 in Kuchroo). Thus, there is no disclosure or suggestion in Kuchroo that compositions such as the claimed compositions would permanently eliminate disease symptoms in all of the treated subjects by preventing T cell activation.

Similarly, some of the experiments described in Karin also involve coinjecting healthy animals with a self antigen and a T cell receptor antagonist peptide. For example, in one

experiment, all rats immunized with the EAE inducer peptide p87-99 developed EAE symptoms, which lasted for 7 days (see Table 2 (p2234). When the rats were coinjected with antagonist peptide, however, none of the rats developed symptoms over the 7 day period. Thus, in contrast to the experiments described in the present invention in which sick animals suffering from autoimmune disease were treated with the claimed compositions, Karin's experiment involved administering T cell antagonist peptides to healthy animals which were not previously suffering from autoimmune disease. In addition, Karin's experiment did not show permanent elimination of disease symptoms, since his experiments covered a span of only 7 days.

In another experiment, Karin induced EAE in rats by injection of p87-99 activated cells (table 3, pg 2235). 2 days after the EAE induction, rats were injected with various peptides and examined daily for EAE symptoms. Animals in this experiment were only followed for 10 days, since EAE resulting from injection of activated cells only lasts for 10 days (See Figure 6 of Karin showing that even in control animals given PBS disease symptoms were eliminated in 10 days). Thus, there is no disclosure or suggestion in Karin that compositions such as the claimed compositions would permanently eliminate disease symptoms in all of the treated subjects by preventing T cell activation.

Furthermore, in contrast to the present compositions, which are designed to suppress immune responses, all of the experiments actually performed by the investigators reviewed in Bona involved the use of immunoglobulins having antigens inserted in the CDR3 regions as vaccines to generate an immune response. While there is some speculation in Bona that self antigens could be inserted into the CDR regions of immunoglobulins to treat autoimmune diseases, there is no disclosure or suggestion in Bona that T cell receptor antagonists could be inserted into immunoglobulins, nor is there any disclosure or suggestion that compositions comprising a T cell receptor antagonist inserted into immunoglobulins could permanently eliminate symptoms in all of the treated subjects by preventing T cell activation.

Because there is no disclosure or suggestion in Bona, Kuchroo, or Karin that immunoglobulins having T cell receptor antagonists inserted therein could permanently eliminate disease symptoms in all of the treated subjects by preventing T cell activation, the present invention is not obvious over the combination of these references.

As discussed in the accompanying Declaration, the claimed compositions permanently eliminated disease symptoms in mice by preventing T cell activation. The data in Exhibit B

demonstrates that 2 month old mice treated with the claimed compositions did not develop disease symptoms for a period of 120 days from administration (i.e. the mice did not develop disease as of approximately 6 months of age). As indicated in the accompanying Declaration, mice have very poor susceptibility to EAE once they reach the age of 24-27 weeks (6 months). Thus, the claimed compositions permanently eliminated disease symptoms.

Furthermore, as indicated in the accompanying Declaration, the permanent elimination of disease symptoms is not a consequence of increased half life. The results shown in Exhibit B of the accompanying Declaration demonstrate that mice treated with the claimed compositions did not develop disease for a period of 15 weeks from administration of the claimed compositions. As indicated in the accompanying Declaration, the half life of immunoglobulins is on the order of 4.5 days. Thus, by 15 weeks from administration, the amount of immunoglobulin remaining in the treated subjects is negligible. As indicated in the accompanying Declaration, it is unlikely that a sufficient amount of the immunoglobulin remains after such an extended time period to provide direct protection from disease. Rather, the observed protection reflects a permanent inactivation of the T cells directed against the antigen responsible for the autoimmune disease.

In addition, Applicant notes that, as indicated in the accompanying Declaration, the claimed compositions prevent T cell activation by binding to newly synthesized MHC molecules after being internalized into the antigen presenting cell. There is no suggestion of this mechanism in Bona, since the actual working examples disclosed in Bona relate to compositions intended to activate an immune response against an antigen embedded in an immunoglobulin rather than to suppress an immune response by preventing T cell activation. Furthermore, as discussed in the accompanying Declaration, the speculation in the Bona reference relating to inserting self-antigens (as opposed to the T cell receptor antagonists used in the claimed compositions) into immunoglobulins indicates that Bona hypothesized that the self antigens would work by preventing pathogenic peptides from binding to MHC proteins so the pathogenic T cells will not be activated. However, under the mechanism hypothesized by Bona, these pathogenic T cells remain potentially harmful as they were not inactivated.

As discussed in the accompanying Declaration, the compositions of Kuchroo and Karin cannot operate via the intracellular mechanism utilized by the claimed compositions, since the compositions of Kuchroo and Karin are free peptides which cannot be internalized and would have to displace other peptides to bind to the MHC proteins on the surface of the antigen

presenting cells. As discussed in the accompanying Declaration, this approach would not be effective because of the unlimited supply of self antigen provided by the host.

In addition, as indicated in the accompanying Declaration and in Exhibit E provided therewith, immunoglobulins containing a T cell receptor antagonist derived from a protein other than proteolipid protein (i.e. T cell receptor antagonists derived from myelin basic protein) were also effective in suppressing autoimmune disease. Thus, compositions comprising an immunoglobulin or portion thereof containing a T cell receptor antagonist are generally effective in treating disease.

In view of the above, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

II. Rejection Based on Provisional Double Patenting

The Examiner further rejected claims 1-7 based on provisional same invention-type double patenting in view of copending application Serial No. 08/779/767. This rejection is contingent upon the issuance of this copending application. While Applicant does not concede that the same invention type double patenting rejection is appropriate, Applicant notes that the copending application has not yet issued. Accordingly, Applicant need not respond to this rejection at the present time.

III. Conclusion

Because the Bona, Kuchroo, and Karin references do not teach or suggest fusion proteins comprising T cell receptor antagonists linked to an immunoglobulin or portion thereof and because these references do not teach or suggest that such fusion proteins would permanently eliminate disease symptoms by preventing T cell activation, applicant respectfully submits that the claims are in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested. Should the Examiner have any questions regarding this matter he is invited to telephone the undersigned so that the questions may be resolved.

The specific changes to the specification and the amended claims are shown on a separate set of pages attached hereto and entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this Amendment. On this set of pages, the insertions are double underlined while the ~~deletions are stricken through~~.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 2, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1 and 4 - 7 have been amended as follows:

1. (Twice Amended) A fusion protein for the alleviation of symptoms associated with an autoimmune disorder comprising an immunoglobulin or portion thereof linked to one or more ~~autoantigenic polypeptides or fragements thereof~~ T cell receptor antagonists wherein said immunoglobulin or portion thereof is capable of binding to an Fc receptor and being endocytosed by an antigen presenting cell to present said one or more T cell receptor antagonists in association with endogenous MHC Class II molecules, thereby preventing T cell activation ~~autoantigenic polypeptides or fragments thereof provides more than one T cell receptor peptide antagonist for presentation on the surface of said antigen presenting cell upon endocytic processing~~.

4. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists alleviates the symptoms ~~autoantigenic polypeptides or fragments thereof is~~ associated with an immune disorder selected from the group consisting of multiple sclerosis, lupis, rheumatoid arthritis, scleroderma, insulin-dependent diabetes and ulcerative colitis.

5. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists is derived from myelin basic protein ~~autoantigenic polypeptides or fragments thereof comprises at least a portion of myelin basic protein~~.

6. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists is derived from proteolipid protein ~~autoantigenic polypeptides or fragments thereof comprises at least a portion of proteolipid protein~~.

7. (Amended) The fusion protein of claim 1 wherein said one or more T cell receptor antagonists is derived from myelin basic protein and from proteolipid protein ~~autoantigenic polypeptides or fragments thereof comprises at least a portion of myelin basic protein and at least a portion of proteolipid protein~~.